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(54) SEMI-SYNTHETIC TAXANES WITH ANTI-TUMOURAL ACTIVITY

SEMISYNTHETISCH TAXAL DERIVATE MIT ANTITUMOR WIRKUNG

TAXANES SEMI-SYNTHETIQUES PRESENTANT UNE ACTIVITE ANTITUMORALE

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- **TETRAHEDRON LETTERS, vol.35, no.19, 1994, OXFORD GB pages 3063 - 3064 E.DIDIER ET AL. 'EXPEDITIOUS SEMISYNTHESIS OF DOCETAXEL' cited in the application**
- **TETRAHEDRON LETTERS, vol.35, no.15, 1994, OXFORD GB pages 2349 - 2352 E.DIDIER ET AL. '2-MONOSUBSTITUTED 1,3-OXAZOLIDINES AS IMPROVED PROTECTIVE GROUPS OF N-BOC-PHENYLISOSERINE IN DOCETAXEL PREPARATION.' cited in the application**

EP 0 773 938 B1

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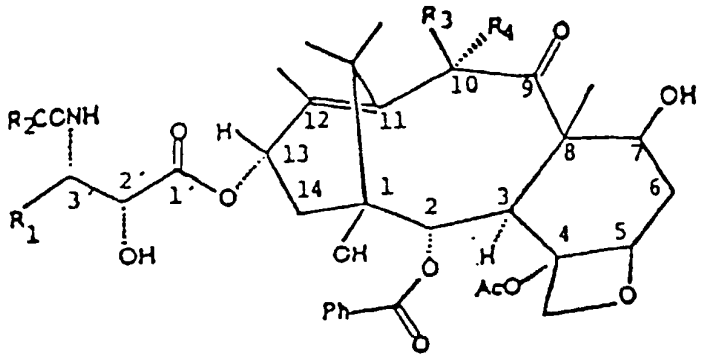
Description

[0001] Diterpenes with taxane skeletons, and in particular taxol, are known to have an anti-tumoural action against numerous human tumours. However, the use of these drugs, particularly taxol, involves some drawbacks due to unwanted side effects. For this reason, and since these anti-tumoural treatments rapidly induce resistance, the development of new molecules whose use reduces the problems observed in clinical use is of interest.

[0002] WO 93/02067 (Nippon Steel) of February 4, 1993, discloses for instance 10-alpha-acetyl-taxol, extracted from tissue culture of albumen of Taxus species, having a marked citotoxic activity.

[0003] The present invention relates to novel taxane-skeleton derivatives obtained by semisynthesis and having a powerful anti-tumoural activity.

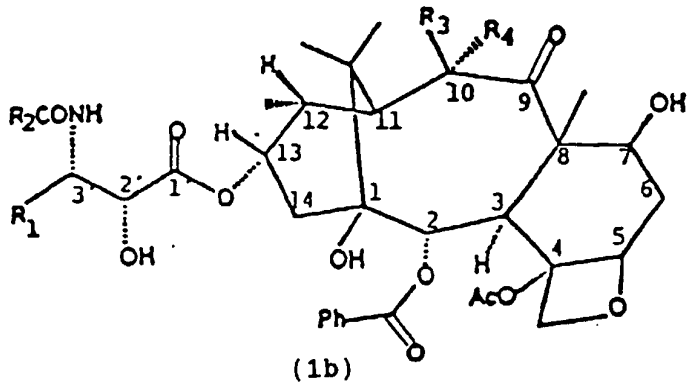
[0004] The derivatives of the invention have formula (**1a**)



(1a)

wherein R_1 = phenyl, R_2 = tert-butoxy, R_3 = H and R_4 = OH.

and formula (**1b**)

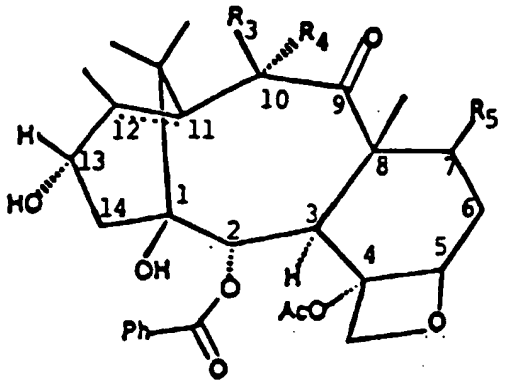


(1b)

wherein R_1 = phenyl, R_2 = tert-butoxy, R_3 = acetoxy and R_4 = H.

[0005] Taxanes of formula (**1a**) and (**1b**) are prepared by esterificating at the 13-position the new syntones of formula (2), using suitably activated isoserine chains as acylating agents, according to what reported in literature for the semisynthesis of taxol and its analogues) (see, for example, EP-A- 400971, 1992, Fr. Dem. 86, 10400; E. Didier et al., Tetrahedron Letters 35, 2349, 1994; E. Didier at al., ibid. **35**, 3063, 1994).

[0006] In formula (2)

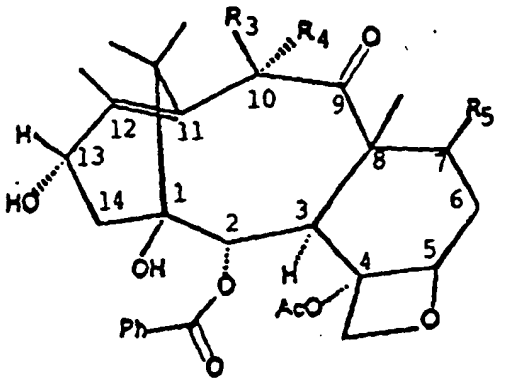


(2)

wherein:

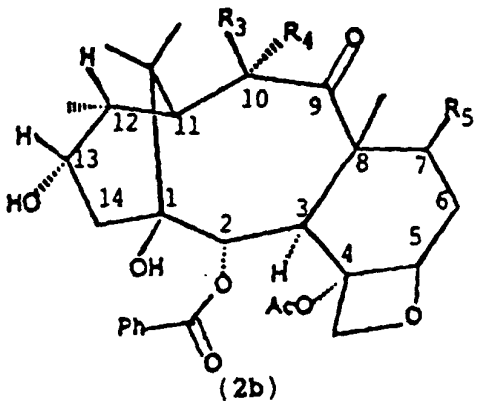
when a double olefinic bond is present at the 11,12-position, R_3 is a hydrogen atom, R_4 and R_5 are hydroxy, C_2-C_8 acyloxy, alkylsilyloxy or 2,2,2-trichloroethoxycarbonyloxy groups;
when a double olefinic bond is not present at the 11,12- position, the methyl at the 12- position is α-oriented, R_4 is a hydrogen atom, R_3 and R_5 are hydroxy, C_2-C_8 acyloxy, alkylsilyloxy or 2,2,2-trichloroethoxycarbonyloxy groups.

[0007] In particular, syntones of formula (**2a**) are used for the synthesis of the novel taxanes of formula (**1a**). On the other hand, syntones of formula (**2b**) are employed for the synthesis of the novel taxanes of formula (**1b**),



(2a)

[0008] In syntones (**2a**), a double olefinic bond is present at the 11,12- position, and a C_2-C_8 acyloxy group or an optionally protected hydroxy group are present at the 10α - position. Therefore, in syntones (**2a**), R_3 is hydrogen, R_4 and R_5 are hydroxy, acyloxy, alkylsilyloxy (such as triethylsilyloxy, O-TES) or 2,2,2-trichloroethoxycarbonyloxy (O-CO-O-CH_2CCl_3, O-TROC) groups.



(2b)

[0009] In syntones (**2b**), the carbon atoms at the 11- and 12- positions are bonded by a single bond, the methyl at the 12- position is α -oriented, and an acyloxy group or an optionally protected hydroxy group are present at the 10a - position. Therefore, in syntones (**2b**), R_4 is hydrogen, R_3 and R_5 are hydroxy, acyloxy, alkylsilyloxy (such as triethylsilyloxy, O-TES) or 2,2,2-trichloroethoxycarbonyloxy (O-CO-O-CH_2CCl_3, O-TROC) groups.

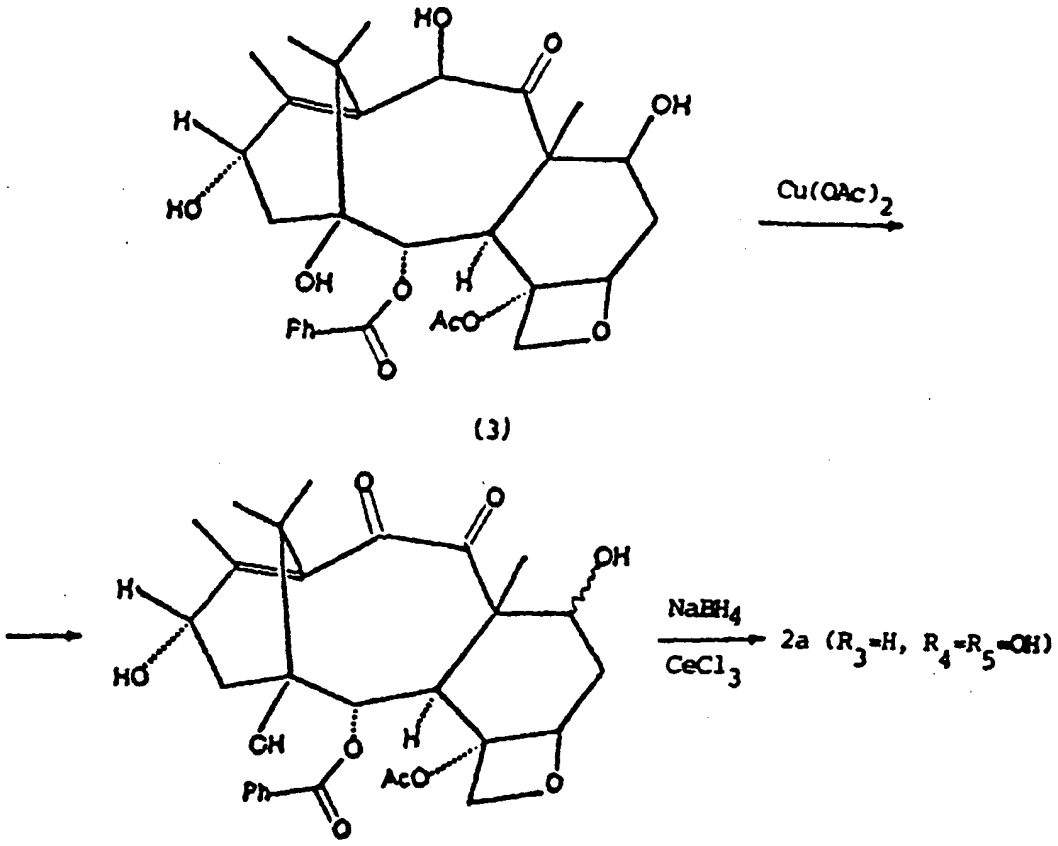
[0010] After esterificating at the 13- position the syntones (2) with the isoserine chain, the protective groups are removed by conventional methods known in literature, thereby obtaining the novel taxanes of Formula (1).

[0011] 10-Deacetylbaccatine III (3), which can be isolated from the leaves of Taxus Baccata (G. Chauvière et coll., C.R. Acad. Sc. Ser. III, 293; 591 [1981]), is used as the sole starting product for the preparation of syntones (**2a**) and (**2b**).

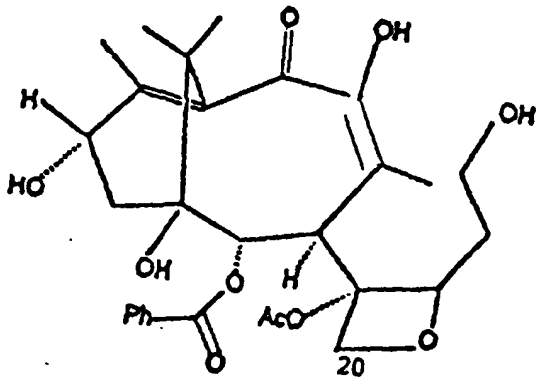
[0012] Syntones of formula (**2a**), which are not known in literature, are obtained (Scheme 1) from (3) by oxidation at the 10- position with copper (II) acetate, to give diketone (**4**), and subsequent reduction with sodium borohydride in the presence of cerium (III) salts.

[0013] The resulting product (**2a**, R_3 = H, R_4 = R_5 = OH), which is the epimer at the 10- position of (**3**), is suitably protected at the 7- and 10- positions and used for the synthesis of taxanes (**1a**).

Scheme 1



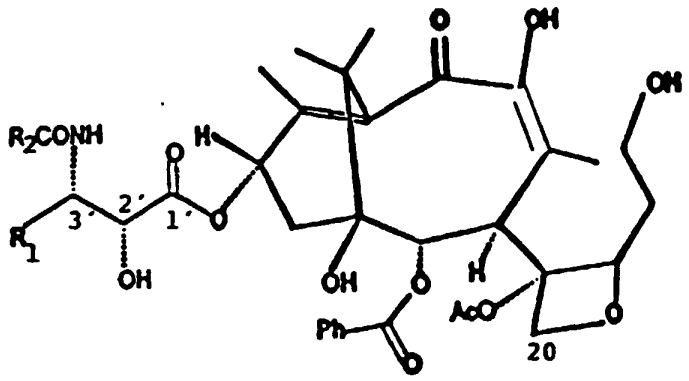
[0014] The new secotaxane (5) is obtained as a by-product of the reaction sequence given in Scheme 1



(5)

[0015] Secotaxane (5) can be used for the synthesis of further taxanes with potential anti-tumoural activity.

[0016] The present invention also relates to novel secotaxane-skeleton derivatives prepared by semisynthesis and having a powerful anti-tumoural activity. Said derivatives have formula (**5a**)



(5a)

wherein:

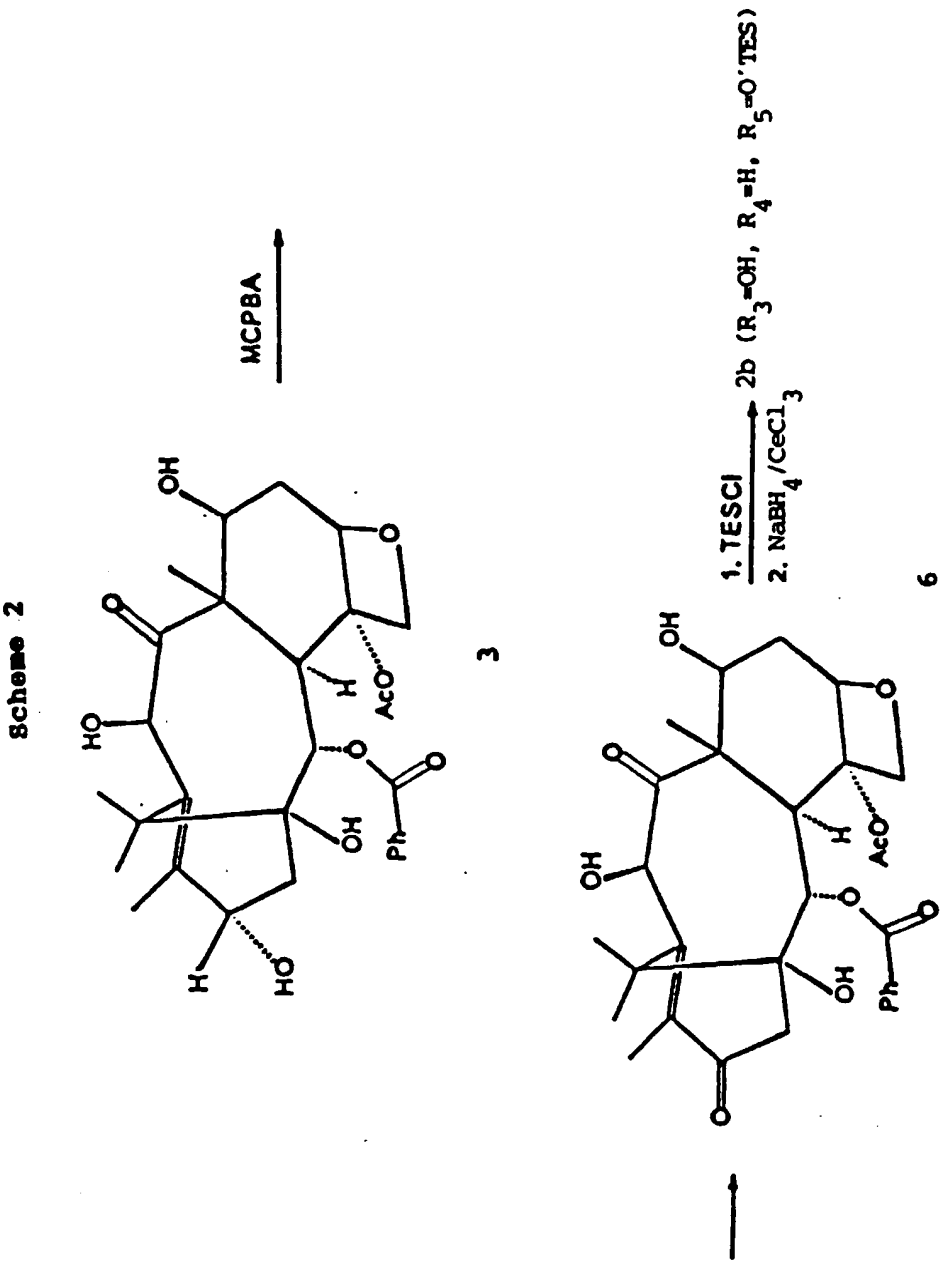
R_1 and R_2, which can be the same or different, are a C_1-C_{20} alkyl, C_2-C_8 alkenyl, aryl (preferably phenyl) or heteroaryl groups. R_2 can also be tert-butoxy.

[0017] Taxanes of formula (**5a**) are prepared by esterificating compound of formula (**5**) in position 13, using the suitably activated isoserine chains as acylating agents, as reported in literature for the semisynthesis of taxol and analogues thereof (see for example EP-A- 400,971; E. Didier et al., Tetrahedron Letters 35, 2349, 1994; E. Didier at al., ibid. 35, 3063, 1994). The hydroxy groups of compound (**5**) can optionally be protected with suitable protective groups, according to conventional methods.

[0018] After the esterification of compound (**5**) at the 13- position with the isoserine chain, the protective groups are removed according to conventional methods known in literature, thereby obtaining secotaxanes of formula (**5a**).

[0019] Syntones of formula (**2b**), which are not known in literature, are also obtained from 10-deacetylbaccatine III (3) (Scheme 2). It has been found that by oxidation of (3) with m-chloroperbenzoic acid (MCPBA), the corresponding 13-ketoderivative (**6**) is obtained. After protecting the hydroxyl at the 7- position with triethylsilyl chloride (TESCl), by reduction with sodium borohydride in the presence of cerium (III) salts, (**6**) gives syntone (**2b**) (R_3 = OH, R_4 = H, R_5 = O-TES), which can be useful for the synthesis of taxanes of formula (**1b**). The α -orientation of the methyl at the 12-position in syntones (**2b**) has been deduced by means of thorough studies using nuclear magnetic resonance.

Scheme 2



[0020] The products of the present invention were screened for their cytotoxic effect on different tumour cell lines, comparing their action with that of taxol. Table 1 shows the IC_{50} data, compared with those found for taxol, of the compounds 13-[(2R, 3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-10-epi-10-deacetylbaccatine III (1a, R_1 = Ph, R_2 =tBuO, R_3 = H, R_4 = OH), 13-[(2R, 3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-10-deacetyl-11,12-dihydrobaccatine III (**1b**, R_1 = Ph, R_2 =tBuO, R_3 = OH, R_4 = H), 13-[(2R, 3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-C-seco-10-deacetylbaccatine III (5a, R_1 = Ph, R_2 = tBuO) and 13-[(2R, 3S)-3-isobutyl-2-hydroxy-3-caproylamino-propanoyl]-C-seco-10-deacetylbaccatine (**5a**, R_1 = isobutyl, R_2 = Pentyl).

Tab. 1 - IC_{50} of taxanes 1a (R_1 = Ph, R_2 = tBuO, R_3 = H, R_4 = OH), 1b (R_1 = Ph, R_2 = tBuO, R_3 = OH, R_4 = H) and of taxol on 6 cell lines.

	Exposure time (h)	Taxol	1a (R_1= Ph, R_2= tBuO, R_3= H, R_4= OH)	1b (R_1= Ph, R_2= tBuO, R_3= OH, R_4= H)
L1210 (murine leukemia)	48	57.0 ± 3.0	46.0 ± 2.1	32.0 ± 0.1
A121 (Human ovarian)	72	3.7 ± 0.3	2.8 ± 0.3	1.6 ± 0.2
A549 (Human NSCLC)	72	5.4 ± 0.5	6.9 ± 0.3	2.1 ± 0.3
HT-29 (Human colon)	72	6.0 ± 0.6	3.4 ± 0.1	3.6 ± 0.4
MCF7 (Human breast)	72	4.3 ± 0.1	2.2 ± 0.2	0.8 ± 0.2
MCF7-ADR (resistant)	72	395.0 ± 8.7	130.0 ± 2.2	128.0 ± 6.2

Standard conditions: substrate RPMI 1640 + 20 mM HEPES + 2 mM L-glutamine.

- (continued) -

EP 0 773 938 B1

Tab. 1 - IC_{50} of taxanes 5a (R_1 = Ph, R_2 = tBuO), 5a (R_1 = isobutyl, R_2 = pentyl) and of taxol on 6 cell lines.

	Exposure time (h)	Taxol	5a (R_1 = Ph, R_2 = tBuO)	5a (R_1 = isobutyl, R_2 = pentyl)
L1210 (murine leukemia)	48	57.0 ± 3.0	35 ± 1,2	26 ± 1,3
A121 (Human ovarian)	72	3.7 ± 0.3	1,9 ± 0,2	1,3 ± 0,1
A549 (Human NSCLC)	72	5.4 ± 0.5	3,3 ± 0,4	2,6 ± 0,3
HT-29 (Human colon)	72	6.0 ± 0.6	3,2 ± 0,3	2,7 ± 0,2
MCF7 (Human breast)	72	4.3 ± 0.1	1,5 ± 0,2	1,1 ± 0,2
MCF7-ADR (resistant)	72	395.0 ± 8.7	31,3 ± 4,2	25,4 ± 3,7

Standard conditions: substrate RPMI 1640 + 20 mM HEPES + 2 mM L-glutamine.

EP 0 773 938 B1

[0021] Compounds with different substituents at the isoserine chain behave similarly. The compounds show surprising advantages over taxol on the cell lines resistant to other anti-tumoural substances such as adriamycin and cisplatinum. The differences between taxol and these products are still more evident in in vivo models, such as athymic nude mouse with human tumour implant. It has also been found that the compounds of the invention in which R_2 is an alkyl or alkenyl group are surprisingly devoid of cardiotoxic activity, unlike taxol and its known derivatives, therefore they can favourably be used in cardiopathic patients untreatable with taxol and its known derivatives.

[0022] The compounds of the invention are suited for incorporation in appropriate pharmaceutical formulations for the parenteral and oral administrations. For the intravenous administration, mixtures of polyethoxylated castor oil and ethanol, or liposomal preparations prepared with natural phosphatidyl choline or mixtures of natural phospholipids in the presence of cholesterol, are mainly used.

[0023] The examples given below further illustrate the invention.

Example 1. Preparation of 10-dehydro-10-deacetylbaccatine III (4).

[0024] 10 g of 10-deacetylbaccatine III (3) are suspended in 350 ml of methanol to which 65 g of $Cu(OAc)_2$ are added. The suspension is continuously stirred at room temperature for 120 hours. The salts are filtered off and the solution is chromatographed on 100 g of silica gel eluting with a 6:4 hexane/ethyl acetate mixture. By crystallisation from ligroin, 9.5 g of (**4**) are obtained, M+ at m/z 542.

Example 2. Preparation of 10-deacetyl-10-epibaccatine III (2a, R_3=H, R_4=R_5=OH) and C-seco-10-deacetylbaccatine III (**5**).

[0025] A solution of 300 mg of (4) in 5 ml of methanol is added with one equivalent of $CeCl_3.3H_2O$, stirred at room temperature for 5 minutes, then added with 80 mg of $NaBH_4$. The solution is treated with a YH_4Cl solution, extracted with ethyl acetate and chromatographed on silica gel eluting with a 3:7 hexane/ethyl acetate mixture. 98 mg of (**2a**) (M+ at m/z 544) and 120 mg of (5) (M+ at m/z 546) are obtained.

[0026] 10-Deacetyl-10-epibaccatine III has the following ^{1}H-NMR spectrum ($CDCl^3$): H2, d 5.68 J 6.8; H3, d 4.26 J 6.8; H5, d 5.03 J 7.1; H7/13, m 4.76; H10, br s 5.20; 10 OH, br s 3.44; H16, s 1.14; H17, s 1.68; H18, s 2.22; H19, s 1.13; H20a, d 4.33; H20b, d 4.18; Ac, s 2.31; Bnz, br 8.12 J 8, br t 7.60 J 8, br t 17.49 J 8.

Example 3. Preparation of 10-deacetyl-13-dehydrobaccatine III (**6**)

[0027] 3 g of meta-chloroperbenzoic acid and 1 g of sodium acetate are added to a suspension of 1 g of 10-deacetylbaccatine III (3) in 100 ml of CH_2Cl_2. The suspension is continuously stirred for 120 hours at room temperature and then diluted with a 5% Na_2CO_3 aqueous solution. The organic phase is washed with 5% Na_2CO_3 and evaporated to dryness. The residue is purified on silica gel eluting with a 3:7 hexane/ethyl acetate mixture. 789 mg of (**6**), M+ at m/z 542 are obtained.

Example 4. Preparation of 10-deacetyl-11,12-dihydro-7-triethylsilyl-baccatine III (**2b**, R_3=OH, R_4=H, R_5=O-TES).

[0028] 1.6 g of (**6**) are dissolved in methylene chloride and added with 370 mg of 4-dimethylaminopyridine and 2.5 ml of triethylsilyl chloride. After 2 hours at room temperature, the reaction mixture is diluted with methylene chloride and washed with water. The organic phase is concentrated to dryness. 1.72 g of a residue is obtained, which is taken up with 150 ml of 95% ethanol and treated with 9 g of $NaBH_4$. After 3 hours the mixture is diluted with a NH_4Cl solution and the product is extracted with ethyl acetate. Following chromatography on silica gel using a 7:3 hexane/ethyl acetate mixture, 800 mg of (**2b**) (R_3=OH, R_4=H, R_5=O-TES) are obtained.

Example 5. Preparation of 11,12-dihydro-7-TES-baccatine III (**2b**, R_3=OH, R_4=H, R_5=O-TES) and 11,12-dihydrobaccatine III (**2b**, R_3=OAc, R_4=H, R_5=OH)

[0029] 500 mg of 10-deacetyl-11,12-dihydro-7-triethylsilylbaccatine III (**2b**, R_3=OH, R_4=H, R_5=O-TES) are reacted in anhydrous pyridine with 3 equivalents of acetyl chloride at 0°C for 6 hours. The reaction mixture is diluted with water and extracted with methylene chloride. After evaporation of the solvent, the residue is crystallised from acetone/hexane. 510 mg of 11,12-dihydro-7-TESbaccatine III are obtained, M+ at m/z 702 III. The product is dissolved in methanol and treated with diluted HCl until complete desilylation. The reaction mixture is diluted with water, extracted with ethyl acetate and crystallisated from aqueous methanol. 400 mg of 11,12-dihydrobaccatine III are obtained, M+ at m/z 588.

Example 6. Preparation of 13-[(2R, 3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-11,12-dihydrobaccatine III (**1b**, R_1=Ph, R_2=tBuO, R_3=OAc, R_4=H).

[0030] 500 mg of 11,12-dihydrobaccatine III (**2b**, R_3=OAc, R_4=H, R_5=O-TES) are dissolved in 20 ml of toluene with 0.45 g of (4S, 5R)-N-tert-butoxycarbonyl-2,2-dimethylphenyl-5-oxazolydinecarboxylic acid, dicyclohexylcarbodiimide (1.03 eq) and N,N-dimethylaminopyridine (0.2 eq) at 80°C for 2 hours. The reaction mixture is washed with water until the excess of the reagents is removed, then concentrated to dryness. The residue is treated with methanol containing 1% formic acid for 4 hours at room temperature. The methanol solution is diluted with water, neutralised and extracted with ethyl acetate. The organic phase is concentrated to dryness and the residue is treated with a solution containing 1.5 eq of di-tert-butyl carbonate and sodium bicarbonate in 15 ml of tetrahydrofuran. The reaction mixture is diluted with water, extracted with ethyl acetate and the heteroacetic phase is concentrated to dryness. The residue is taken up with acidic methanol by hydrochloric acid to complete desilylation. The solution is then diluted with water and extracted with ethyl acetate. The residue obtained by evaporation of the heteroacetic phase is chromatographed on silica gel eluting with a 1:1 acetone/hexane mixture to remove the reaction impurities. 580 mg of product are obtained, M+ at m/z 851.

Example 7. Preparation of 13-[(2R, 3S)-3-benzoylamino-3-phenyl-2-hydroxypropanoyl]-11,12-dihydrobaccatine III (**1b**, R_1=R_2=Ph, R_3=OAc, R_4=H).

[0031] 500 mg of 11,12-dihydro-7-TES-baccatine (2b, R_3=OAc, R_4=H, R_5=O-TES) are dissolved in 20 ml of toluene together with 1.5 g of (4S, 5R)-Y-benzoyl-2,2-dimethyl-4-phenyl-5-oxazolydinecarboxylic acid, dicyclohexylcarbodiimide (1.03 eq) and N,N-dimethylaminopyridine (0.2 eq) at 80°C for 2 hours. The reaction mixture is washed with water until the excess of reagents is removed, then concentrated to dryness. The residue is treated with methanol containing 1% formic acid for 4 hours at room temperature. The methanol solution is diluted with water, neutralised and extracted with ethyl acetate. The organic phase is concentrated to dryness and the residue is taken up with methanol acidic by hydrochloric acid to complete desilylation. The solution is then diluted with water and extracted with ethyl acetate. The residue obtained by evaporation of the heteroacetic phase is chromatographed on silica gel eluting with a 1:1 acetone/hexane mixture to remove the reaction impurities. 530 mg of product are obtained, M+ at m/z 855.

Example 8. Preparation of 13-[(2R, 3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-10-epi-10-deacetylbaccatine III (**1a**, R_1=Ph, R_2=tBuO, R_3=H, R_4=OH).

[0032] 500 mg of 10-deacetyl-10-epibaccatine III (**2a**, R_3=H, R_4=R_5=OH) are dissolved in 15 ml of anhydrous pyridine and treated for 5 minutes at 80°C with three equivalents of trichloroethoxycarbonyl chloride (TROC-Cl) and then cooled to room temperature. 1 ml of methanol is added to decompose the excess TROC-Cl. The solution is diluted with iced water and extracted with chloroform, washing the organic phase with a hydrochloric acid diluted solution. The organic phase is evaporated to dryness and the residue is treated at room temperature for 24 hours with a toluene solution containing three equivalents of (4S, 5R)-N-tertbutoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolydinecarboxylic acid, 3 equivalents of dicyclohexylcarbodiimide and 0.2 equivalents of N,N-dimethylaminopyridine. The reaction mixture is washed with water and the organic phase is evaporated to dryness under vacuum. The residue is taken up with methanol and treated with one equivalent of p-toluenesulfonic acid for 48 hours, after that is diluted with water and extracted with ethyl acetate. The organic phase is evaporated under vacuum and the residue is taken up in 200 ml of a 1:1 acetic acid/ethyl acetate mixture and treated for 3 hours at 30°C with 11 equivalents of powdered zinc. The solid material is filtered off and the solution is diluted with water, extracted with ethyl acetate and chromatographed on silica gel eluting with a 1:4 ethyl acetate/hexane mixture. 512 mg of product (Ia) are obtained, M+ at m/z 807.

Example 9. Preparation of 7,9-ditriethylsilyl-C-seco-10-deacetylbaccatine III

[0033] A solution of (5) (200 mg, 0.37 mmol) in anhydrous dimethylformamide (DMF) (5 ml), is added with imidazole (75 mg, 1.11 mmol, 3 eq. mol) and triethylsilyl chloride (TES) (186 ml, 167.3 mg, 1.11 mmol, 3 eq. mol) and the reaction mixture is stirred for 10 minutes at room temperature. The reaction is checked by TLC (3:7 hexane-ethyl acetate, Rf of the starting material 0.10, Rf of the product 0.80). The reaction is quenched by addition of water and Celite®, and the precipitate is filtered and washed with water to remove DMF, then with $CHCl_3$ to remove the product. After purification by column chromatography (9:1 hexane/ethyl acetate to elute silanol, then 6:4 hexane/ethyl acetate to elute the product) 146 mg of the title product are obtained (51%).

Example 10. Preparation of 13-[(2R,3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl-C-seco-10-deacetylbaccatine III (**5a**, R_1=Ph, R_2=tBuO).

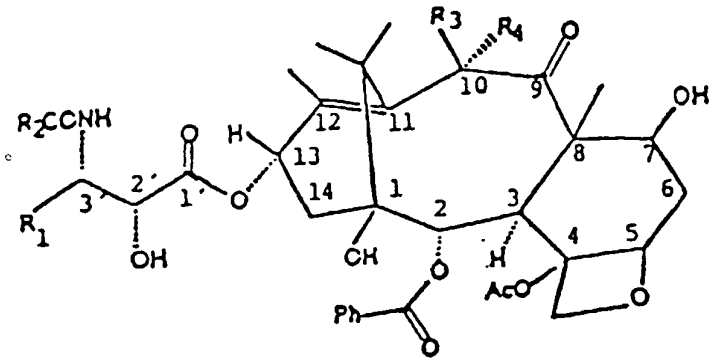
[0034] A solution of the product obtained in example 9 (126 mg, 0.16 mmol) in anhydrous toluene (5 ml), is added with 67.5 mg of dicyclohexylcarbodiimide (0.327 mmol, 2 mol. eq.), 105 mg of (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic (0.327 mmol, 2 mol eq.) and 5 mg of 4-dimethylaminopyridine. The mixture is heated to 60°C for 24 hours and diluted with a $NaHCO_3$ saturated aqueous solution and ethyl acetate. The residue is purified by column chromatography (8:2 hexane-ethyl acetate) to give 175 mg of the 13-ester (95%). The residue is taken up with 50 ml of methanol/HCl (0.01%) and the reaction mixture is left at room temperature for 1 hour. The solution is alkalinized to pH 5 and concentrated to dryness under vacuum. The residue is chromatographed on a silica gel column eluting with a 98:2 methylene chloride-methanol mixture. After crystallization from ethyl acetate, 85 mg of the title compound are obtained.

Example 11. Preparation of 13-[(2R,3S)-3-isobutyl-2-hydroxy-3-caproylamino-propanoyl-C-seco-10-deacetylbaccatine III (5a, R_1-isobutyl, R_2 = pentyl).

[0035] A solution of the product obtained in example 9 (126 mg, 0.16 mmol) in anhydrous toluene (5 ml), is added with 67.5 mg of dicyclohexylcarbodiimide (0.327 mmol, 2 mol. eq.), 140 mg of (4S,5R)-N-caproyl-2-(2,4-dimethoxyphenyl)-4-isobutyl-5-oxazolidinecarboxylic acid (0,327 mmol, 2 mol eq.) and 5 mg of 4-dimethylaminopyridine. The mixture is heated to 60°C for 24 hours and diluted with a $YaHCO_3$ saturated aqueous solution and ethyl acetate. The residue is purified by column chromatography (8:2 hexane-ethyl acetate) to give 175 mg of the 13-ester (95%). The residue is taken up with 50 ml of methanol/HCl (0.01%) and the reaction mixture is left at room temperature for 1 hour. The solution is alkalinized to pH 5 and concentrated to dryness under vacuum. The residue is chromatographed on a silica gel column eluting with a 98:2 methylene chloride-methanol mixture. After crystallization from ethyl acetate, 88 mg of the title compound are obtained.

Claims

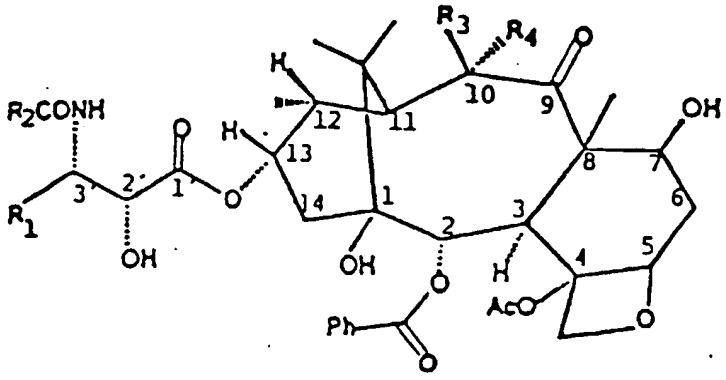
1. The compound 13-[(2R, 3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-10-epi-10-deacetylbaccatine III, of formula (**1a**)



(1a)

wherein R_1 = phenyl, R_2 = tert-butoxy, R_3 = H, R_4 = OH.

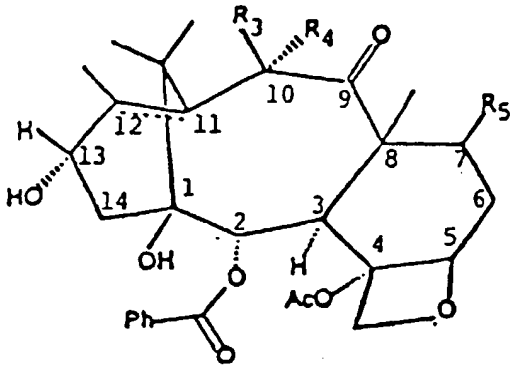
2. The compound 13-[(2R, 3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-11,12-dihydrobaccatine III, of formula (**1b**)



(1b)

where R_1 = phenyl, R_2 = tert-butoxy, R_3 = acetoxy and R_4 = H.

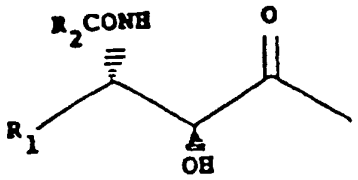
3. A process for the preparation of the compounds of claims 1 and 2, in which process syntones of formula (2)



(2)

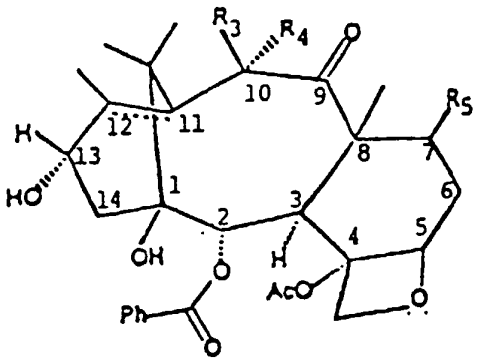
wherein:

when a double olefinic bond is present in position 11,12, R_3 is hydrogen, R_4 and R_5 are hydroxy, C_2-C_8-acyloxy, alkylsilyloxy or 2,2,2-trichloroethoxycarbonyloxy groups;
when a double olefinic bond is not present in position 11,12, the methyl in position 12 is α -oriented, R_4 is hydrogen, R_3 and R_5 are hydroxy, C_2-C_8-acyloxy, alkylsilyloxy or 2,2,2-trichloroethoxycarbonyloxy groups;
are subjected to esterification, according to known methods, with suitably activated and/or protected isoserine derivatives, thereby introducing the acyl group in position 13.



(where R_1 and R_2 have the meanings as in claims 1 and 2),
and the protective groups are subsequently removed according to known methods.

4. As an intermediate, a compound of formula (2)

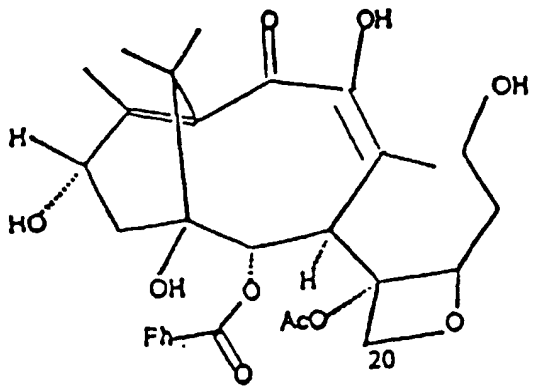


(2)

wherein:

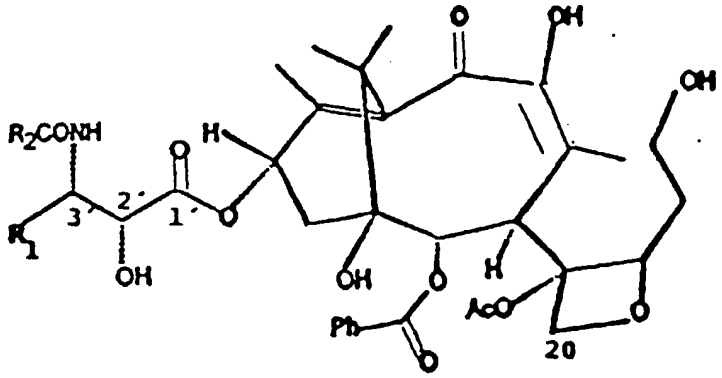
when a double olefinic bond is present in position 11,12, R_3 is hydrogen, R_4 and R_5 are hydroxy, C_2-C_8-acyloxy, alkylsilyloxy or 2,2,2-trichloroethoxycarbonyloxy groups;
when a double olefinic bond is not present in position 11,12, the methyl in position 12 is α -oriented, R_4 is a hydrogen atom, R_3 and R_5 are hydroxy, C_2-C_8-acyloxy, alkylsilyloxy or 2,2,2-trichloroethoxycarbonyloxy groups.

5. As an intermediate, a compound of formula (5)



(5)

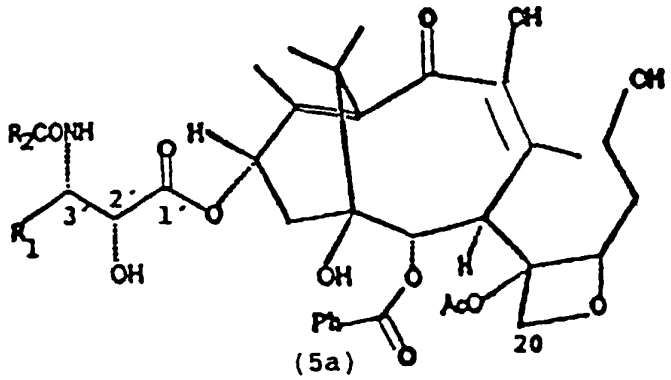
6. A semisynthetic secotaxane of formula **5a**



(5a)

wherein:
R_1 and R_2, which can be the same or different, are a C_1-C_{20} alkyl, C_2-C_8 alkenyl, aryl or heteroaryl group, R_2 can also be a tert-butoxy group.

7. As compound according to claim 6, 13-[(2R,3S)-3-phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-C-seco-10-deacetylbaccatine III, of formula 5a

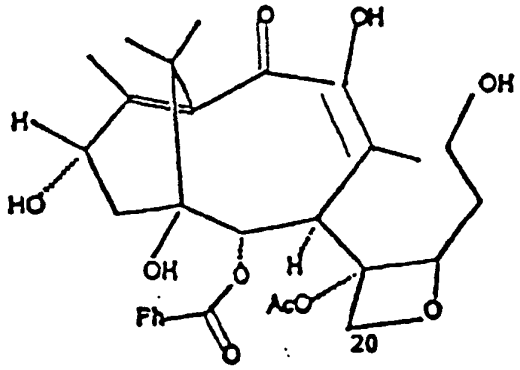


(5a)

wherein R_1 = phenyl, R_2 = tert-butoxy.

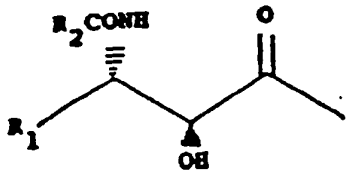
8. As compound according to the claim 6, 13-[(2R,3S)-3-isobutyl-2-hydroxy-3-caproylamino-propanoyl-C-seco-10-deacetylbaccatine III of formula 5a wherein R_1=isobutyl, R_2 = pentyl.

9. A process for the preparation of the compounds according to claim 6, wherein compound of formula 5



(5)

is subjected to esterification, according to conventional methods, with derivatives suitably activated and/or protected at the isoserine chain, thereby introducing the acyl group in the 13-position



(wherein R_1 and R_2 have the meanings defined in claim 6),
thereafter removing the protective groups, according to conventional methods.

10. Pharmaceutical compositions containing taxanes according to claims 1-2 and 6-8.

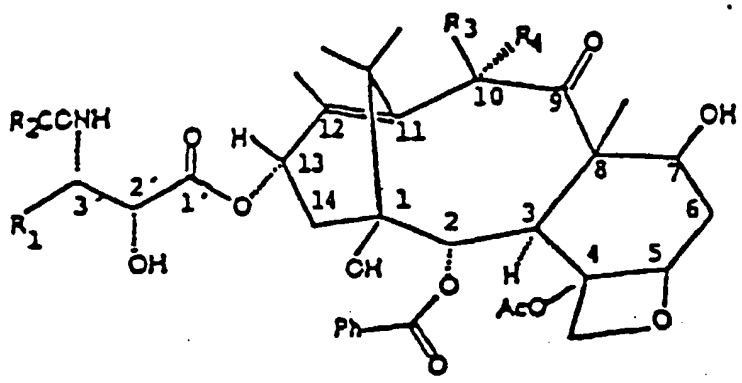
11. Pharmaceutical compositions according to claim 10 having anti-tumoural action.

12. The use of taxanes according to claims 1-2 and 6-8 for the preparation of medicaments useful for the treatment of cancer.

13. The use of taxanes according to claim 6, wherein R_2 is an alkyl or alkenyl group, for the preparation of medicaments useful for the treatment of cancer in cardiopathic patients.

Patentansprüche

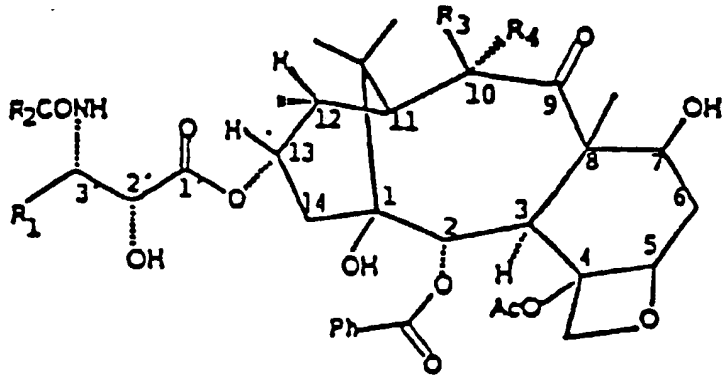
1. Verbindung 13-[(2R,3S)-3-Phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-10-epi-10-desacetylbaccatin III der Formel (1a)



(1a)

worin R_1 = Phenyl, R_2 = tert-Butoxy, R_3 = H, R_4 = OH.

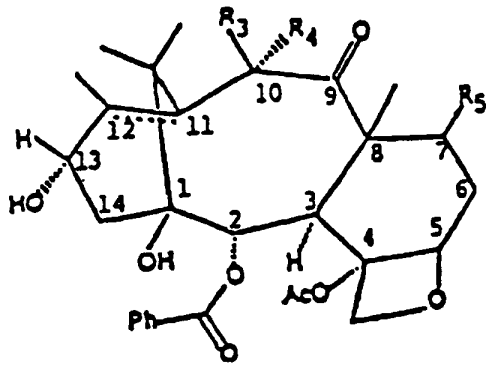
2. Verbindung 13-[(2R,3S)-3-Phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-11,12-dihydrobaccatin III der Formel (1b)



(1b)

worin R_1 = Phenyl, R_2 = tert-Butoxy, R_3 = Acetoxy und R_4 = H.

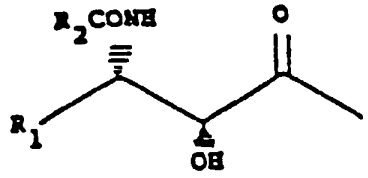
3. Verfahren zur Herstellung der Verbindungen von Ansprüchen 1 und 2, wobei in dem Verfahren Synthone der Formel (2)



(2)

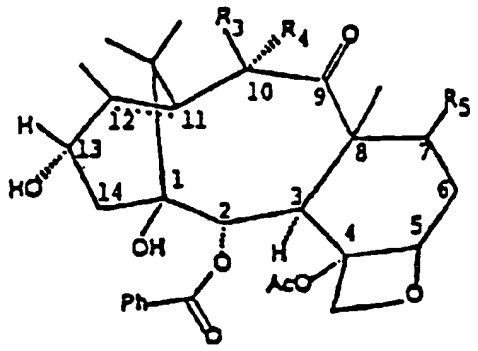
worin:

wenn eine olefinische Doppelbindung in Stellung 11,12 vorliegt, R_3 ein Wasserstoffatom ist, R_4 und R_5 Hydroxy-, C_2-C_8-Acyloxy-, Alkylsilyloxy- oder 2,2,2-Trichlorethoxycarbonyloxygruppen sind;
wenn keine olefinische Doppelbindung in Stellung 11,12 vorliegt, die Methylgruppe in Stellung 12 α-orientiert ist, R_4 ein Wasserstoffatom ist, R_3 und R_5 Hydroxy-, C_2-C_8-Acyloxy-, Alkylsilyloxy- oder 2,2,2-Trichlorethoxycarbonyloxygruppen sind;
gemäß bekannter Verfahren mit geeignet aktivierten und/oder geschützten Isoserinderivaten verestert werden, wodurch die Acylgruppe



(worin R_1 und R_2 die gleichen Bedeutungen wie in Ansprüchen 1 und 2 aufweisen) in Stellung 13 eingeführt wird,
und die Schutzgruppen anschließend gemäß bekannter Verfahren entfernt werden.

4. Verbindung der Formel (2)

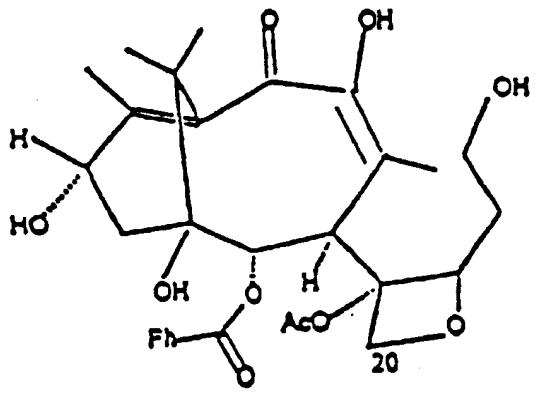


(2)

worin:

wenn eine olefinische Doppelbindung in Stellung 11,12 vorliegt, R_3 ein Wasserstoffatom ist, R_4 und R_5 Hydroxy-, C_2-C_8-Acyloxy-, Alkylsilyloxy- oder 2,2,2-Trichlorethoxycarbonyloxygruppen sind;
wenn keine olefinische Doppelbindung in Stellung 11,12 vorliegt, die Methylgruppe in Stellung 12 α-orientiert ist, R_4 ein Wasserstoffatom ist, R_3 und R_5 Hydroxy-, C_2-C_8-Acyloxy-, Alkylsilyloxy- oder 2,2,2-Trichlorethoxycarbonyloxygruppen sind, als Zwischenprodukt.

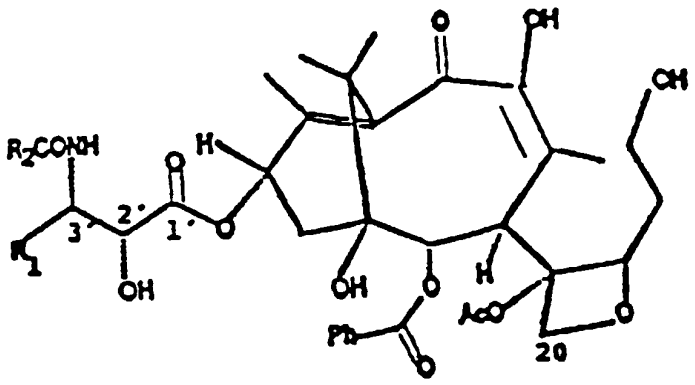
5. Verbindung der Formel (5)



(5)

als Zwischenprodukt.

6. Halbsynthetisches Secotaxane der Formel 5a

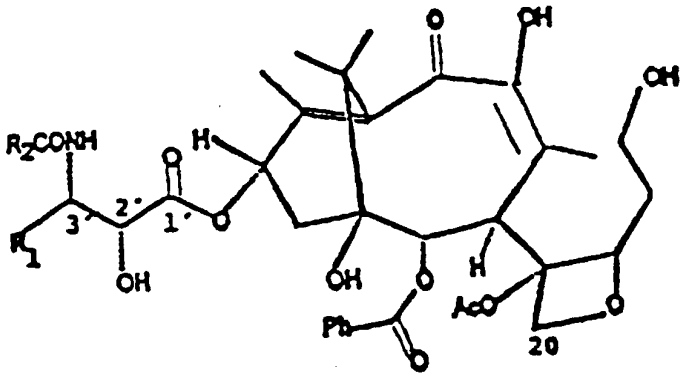


(5a)

worin

R_1 und R_2, die gleich oder verschieden sein können, eine C_1-C_{20}-Alkyl-, C_2-C_8-Alkenyl-, Aryl- oder Heteroarylgruppe darstellen, wobei R_2 ebenfalls eine tert-Butoxygruppe sein kann.

7. Verbindung nach Anspruch 6, nämlich 13-[(2R,3S)-3-Phenyl-2-hydroxy-3-tert-butoxycarbonylamino-propanoyl]-C-seco-10-desacetylbaccatin III der Formel 5a

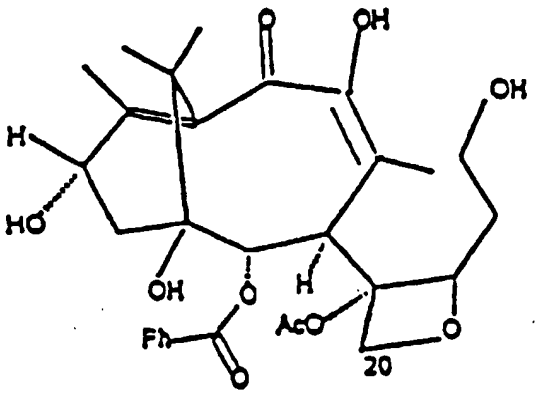


(5a)

worin R_1 = Phenyl, R_2 = tert-Butoxy.

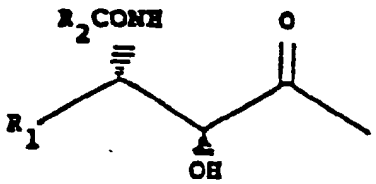
8. Verbindung nach Anspruch 6, nämlich 13-[(2R,3S)-3-Isobutyl-2-hydroxy-3-caproylamino-propanoyl]-C-seco-10-desacetylbaccatin III der Formel 5a, worin R_1 = Isobutyl, R_2 = Pentyl.

9. Verfahren zur Herstellung von Verbindungen nach Anspruch 6, wobei eine Verbindung der Formel 5



(5)

gemäß üblicher Verfahren mit Derivaten, die an der Isoserinkette geeignet aktiviert und/oder geschützt sind, verestert wird, wodurch die Acylgruppe



(worin R_1 und R_2 die gleichen Bedeutungen wie in Anspruch 6 aufweisen) in Stellung 13 eingeführt wird, anschließend Entfernen der Schutzgruppen gemäß üblicher Verfahren.

10. Pharmazeutische Zusammensetzungen, die Taxane nach Ansprüchen 1-2 und 6-8 enthalten.

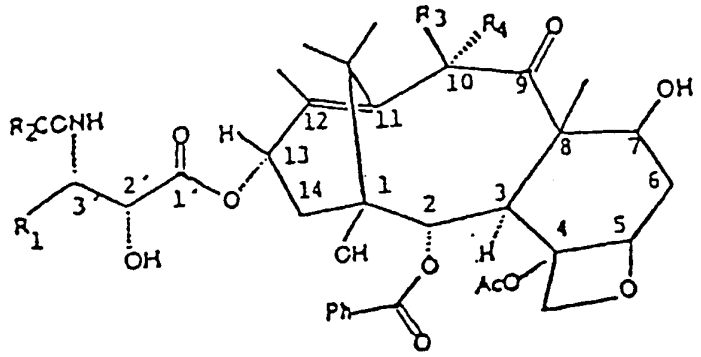
11. Pharmazeutische Zusammensetzungen nach Anspruch 10 mit Antitumorwirkung.

12. Verwendung von Taxanen nach Ansprüchen 1-2 und 6-8 zur Herstellung von Arzneimitteln, die zur Behandlung von Krebs verwendbar sind.

13. Verwendung von Taxanen nach Anspruch 6, wobei R_2 eine Alkyl- oder Alkenylgruppe darstellt, zur Herstellung von Arzneimitteln, die zur Behandlung von Krebs bei herzkranken Patienten verwendbar sind.

Revendications

1. Composé 13-[(2R,3S)-3-phényl-2-hydroxy-3-tert.-butoxycarbonylamino-propanoyl]-10-épi-10-désacétylbaccatine III, de formule (1a) :

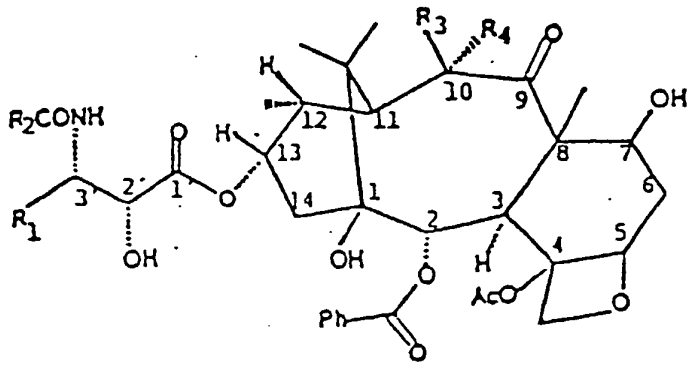


(1a)

dans laquelle :

- R_1 = phényle ;
- R_2 = tert.-butoxy ;
- R_3 = H ;
- R_4 = OH.

2. Composé 13-[(2R,3S)-3-phényl-2-hydroxy-3-tert.-butoxycarbonylamino-propanoyl]-11,12-dihydrobaccatine III, de formule (1b) :

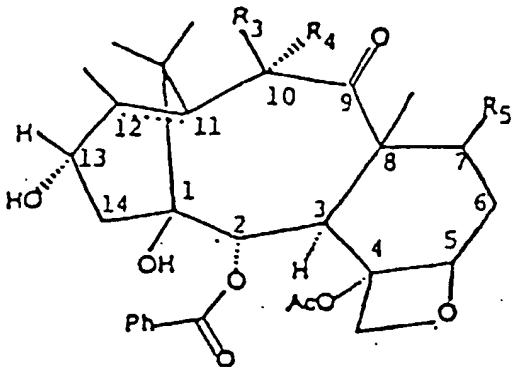


(1b)

dans laquelle :

- R_1 = phényle ;
- R_2 = tert.-butoxy ;
- R_3 = acétoxy ; et
- R_4 = H.

3. Procédé de préparation des composés définis aux revendications 1 et 2, dans lequel des syntons de formule (2) :

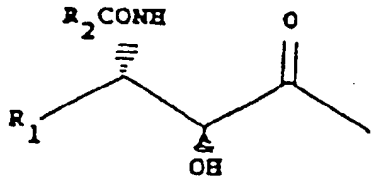


(2)

dans laquelle :

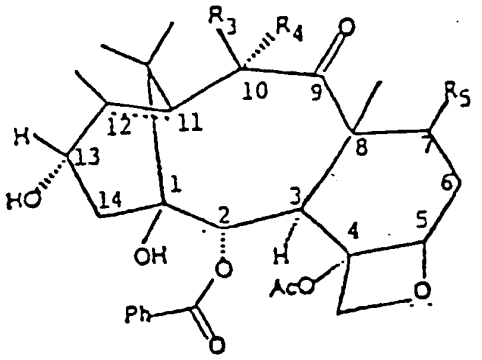
- lorsque une double liaison oléfinique est présente en positions 11,12, R_3 représente hydrogène, R_4 et R_5 représentent des groupes hydroxy, acyloxy en C_2-C_8, alkylsilyloxy ou 2,2,2-trichloroéthoxycarbonyloxy ;
- lorsqu'il n'y a pas de double liaison oléfinique en positions 11,12, le méthyle en position 12 est à orientation α, R_4 représente hydrogène, R_3 et R_5 représentent des groupes hydroxy, acyloxy en C_2-C_8, alkylsilyloxy ou 2,2,2-trichloroéthoxycarbonyloxy ;

sont soumis à une estérification, conformément à des méthodes connues, par des dérivés isosérine, activés et/ou protégés de façon appropriée, permettant ainsi d'introduire le groupe acyle en position 13,



(où R_1 et R_2 ont les mêmes significations que dans les revendications 1 et 2),
et les groupes protecteurs sont ensuite éliminés conformément à des méthodes connues.

4. En tant qu'intermédiaire, un composé de formule (2) :

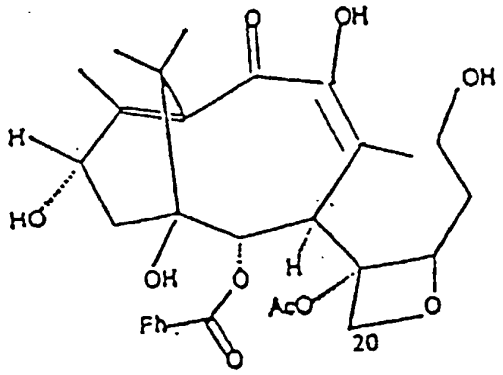


(2)

dans laquelle :

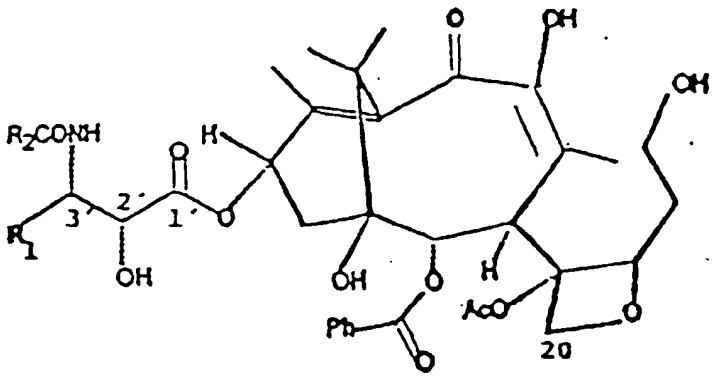
- lorsque une double liaison oléfinique est présente en positions 11,12, R_3 représente hydrogène, R_4 et R_5 représentent des groupes hydroxy, acyloxy en C_2-C_8, alkylsilyloxy ou 2,2,2-trichloroéthoxycarbonyloxy ;
- lorsqu'il n'y a pas de double liaison oléfinique en positions 11,12, le méthyle en position 12 est à orientation α, R_4 représente un atome d'hydrogène, R_3 et R_5 représentent des groupes hydroxy, acyloxy en C_2-C_8, alkylsilyloxy ou 2,2,2-trichloroéthoxycarbonyloxy.

5. En tant qu'intermédiaire, un composé de formule (5) :



(5)

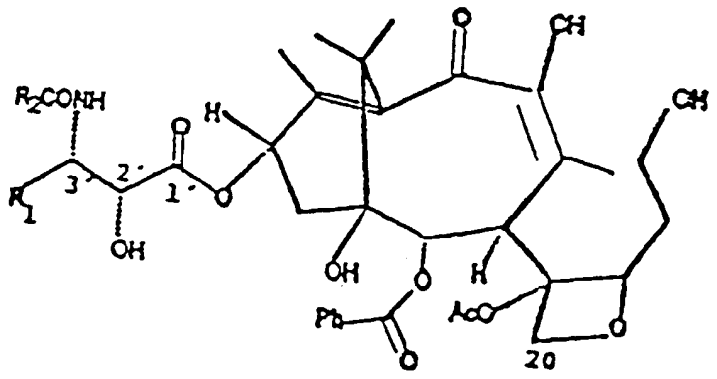
6. Sécotaxane semisynthétique de formule (5a) :



(5a)

dans laquelle R_1 et R_2, qui peuvent être identiques ou différents, représentent un groupe alkyle en C_1-C_{20}, alcényle en C_2-C_8, aryle ou hétéroaryle, R_2 pouvant aussi être un groupe tert.-butoxy.

7. En tant que composé selon la revendication 6, la 13-[(2R,3S)-3-phényl-2-hydroxy-3-tert.-butoxycarbonylamino-propanoyl]-C-séco-10-désacétylbaccatine III, de formule 5a :



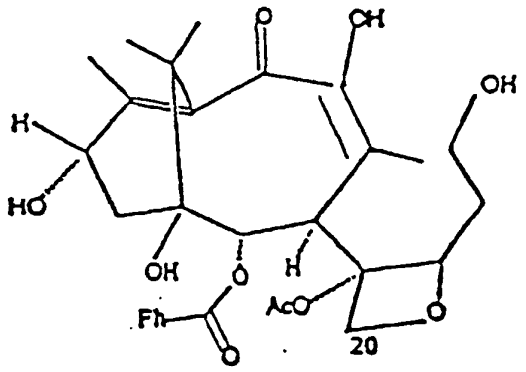
(5a)

dans laquelle :

- R_1 = phényle ; et
- R_2 = tert.-butoxy.

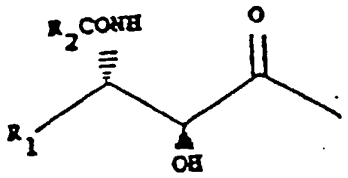
8. En tant que composé selon la revendication 6, la 13-[(2R,3S)-3-isobutyl-2-hydroxy-3-caproylaminopropanoyl-C-séco-10-désacétylbaccatine III de formule 5a dans laquelle R_1= isobutyle, R_2 = pentyle.

9. Procédé de préparation des composés définis à la revendication 6, dans lequel le composé de formule (5) :



(5)

est soumis à une estérification, conformément à des méthodes classiques, par des dérivés activés et/ou protégés de façon appropriée au niveau de la chaîne isosérine, en introduisant de cette façon le groupe acyle en position 13,



(dans laquelle R_1 et R_2 ont les significations définies à la revendication 6),
en éliminant par la suite les groupes protecteurs, conformément à des méthodes classiques.

10. Compositions pharmaceutiques contenant des taxanes tels que définis aux revendications 1 - 2 et 6 - 8.

11. Compositions pharmaceutiques selon la revendication 10, ayant une action anti-tumorale.

12. Utilisation des taxanes définis aux revendications 1 - 2 et 6 - 8 pour la préparation de médicaments utiles pour le traitement du cancer.

13. Utilisation des taxanes définis à la revendication 6, dans laquelle R_2 représente un groupe alkyle ou alcényle, pour la préparation de médicaments utiles pour le traitement du cancer chez des patients cardiopathiques.